University of Groningen

A new poly(1,3-trimethylene carbonate) film provides effective adhesion reduction after major abdominal surgery in a rat model

Vogels, Ruben R. M.; Bosmans, Joanna W. A. M.; van Barneveld, Kevin W. Y.; Verdoold, Vincent; van Rijn, Selwyn; Gijbels, Marion J. J.; Penders, John; Breukink, Stephanie O.; Grijpma, Dirk W.; Bouvy, Nicole D.

Published in:
Surgery

DOI:
10.1016/j.surg.2015.02.004

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Vogels, R. R. M., Bosmans, J. W. A. M., van Barneveld, K. W. Y., Verdoold, V., van Rijn, S., Gijbels, M. J. J., Penders, J., Breukink, S. O., Grijpma, D. W., & Bouvy, N. D. (2015). A new poly(1,3-trimethylene carbonate) film provides effective adhesion reduction after major abdominal surgery in a rat model. *Surgery*, *157*(6), 1113-1120. https://doi.org/10.1016/j.surg.2015.02.004

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

A new poly(1,3-trimethylene carbonate) film provides effective adhesion reduction after major abdominal surgery in a rat model

Ruben R. M. Vogels, MD,[a,b] Joanna W. A. M. Bosmans, MD,[a,b] Kevin W. Y. van Barneveld, MD,[a,b] Vincent Verdoold, MSc,[c,d] Selwyn van Rijn, MD,[a,b] Marion J. J. Gijbels, PhD,[e] John Penders, PhD,[f] Stephanie O. Breukink, MD, PhD,[a] Dirk W. Grijpma, PhD,[c,g] *and* **Nicole D. Bouvy, MD, PhD,[a,b]**
Maastricht, Enschede, Ede, and Groningen, The Netherlands

Background. *Postoperative adhesions remain a major clinical problem after abdominal surgery. We evaluated the efficacy of a new poly(trimethylene carbonate) (PTMC) film as an antiadhesive material. In many abdominal operations, there is an increased risk of fecal contamination; the risk of (increased) infection in presence of PTMC film was studied in 2 additional animal models.*
Methods. *A validated rat adhesion model with peritoneal ischemic buttons was used to compare the new PTMC film with a hyaluronate carboxymethylcellulose (HA-CMC) sheet, icodextrin solution, and a control group. Primary endpoint was occurrence of adhesions at the ischemic buttons after 14 days in 44 rats (*n *= 11 per group). To evaluate potential risks associated with the film, both an anastomotic leakage model and a cecal ligation and puncture model were used. Kruskal–Wallis tests with subsequent Mann–Whitney tests were used to detect differences between groups.*
Results. *PTMC film showed a significant reduction in the amount of adhesions (median, 0.5 buttons) compared with control group (median, 4 buttons;* $P < .001$*) and icodextrin group (median, 4.5;* $P < .001$*). The amount of adhesions was similar to the HA-CMC group (median, 2;* $P = .04$*). The presence of the film did not increase the risk of anastomotic leakage or bacterial growth in a contaminated environment.*
Conclusion. *The presence of a PTMC film leads to a significant reduction in the amount of adhesions after 14 days in an ischemic button rat model. Furthermore, this film was found to be safe in an animal model, even in complex abdominal operations with an increased risk of fecal contamination. (Surgery 2015;157:1113-20.)*

From the Department of General Surgery,[a] and the NUTRIM School for Nutrition, Toxicology and Metabolism,[b] Maastricht University, Maastricht; MIRA Institute for Biomedical Technology and Technical Medicine, and Department of Biomaterials Science and Technology, Faculty of Science and Technology,[c] University of Twente, Enschede; Medisse BV,[d] Ede; Departments of Pathology[e] and Medical Microbiology,[f] Maastricht University Medical Centre, Maastricht; and Department of Biomedical Engineering,[g] W.J. Kolff Institute, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Adhesion formation after abdominal surgery is a major clinical problem, with an incidence of >93% of all patients undergoing laparotomy.[1-3] These postoperative adhesions are associated with many short- and long-term postoperative complications and lead to readmission of one in 3 patients

R.R.M.V. and J.W.A.M.B. contributed equally to this manuscript.

Disclosure: This research received funding from Medisse BV, Ede, The Netherlands, for acquisition of required materials, animals, and associated costs. Authors R.R.M.V., J.W.A.M.B., K.W.Y.v.B., S.O.B., G.B., and N.D.B. declare no conflict of interest, are all employed by academic medical centers, and have no financial ties to Medisse BV. V.V. produced the PTMC films used in the experiments, but was not involved with acquisition and interpretation of experimental results. D.G. holds a position in the advisory board of Medisse BV and receives no financial support from the company, but has stock options.

Accepted for publication February 13, 2015.

Reprint requests: Ruben R. M. Vogels, MD, Department of General Surgery, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ, Maastricht, The Netherlands. E-mail: r.vogels@maastrichtuniversity.nl.

0039-6060/$ - see front matter

© 2015 Elsevier Inc. All rights reserved.

http://dx.doi.org/10.1016/j.surg.2015.02.004

within the first 10 years.[2-4] Unfortunately, the appearance of adhesion formation remains as an underestimated clinical problem.[5-7] Many different materials have been developed for the prevention of postoperative adhesions.[8-10] Of these materials, mainly the "barrier-type" materials, like hyaluronate carboxymethylcellulose (HA-CMC; Seprafilm, Genzyme Biosurgery, Sanofi, The Netherlands) have been found to be effective in reducing the amount of severe adhesions.[8,11,12] Results of "liquid-based" adhesion prevention, such as intraperitoneal administration of icodextrin (Adept), are still inconclusive.[10,12,13]

Barrier materials are believed to work by providing an inert and inactive barrier between tissues to reduce adhesion formation without providing bioactive properties, allowing the peritoneum to heal, while inducing minimal foreign body reaction.[14,15] Although these materials show a significant reduction in the number of adhesions, we believe these results can be improved by using a more stable barrier material. This could be achieved by using poly(trimethylene carbonate) (PTMC), an inert, slow degrading polymer with excellent biocompatibility.[16] In addition, it was shown that the polymer is phagocytized by macrophages and that at 12 weeks PTMC is degraded, whereas only a small area of inflammatory cells could be observed at the site of implantation.[16,17] Unlike other materials that can be used to produce membrane, such as collagen, this polymer degrades through surface degradation, allowing it to retain its mechanical characteristics throughout the degradation process.[16-18] Furthermore, in bone regeneration studies, PTMC promoted bone healing without leading to osseous depositions inside the film owing to solid composition, in contrast with collagenous membranes.[17] This led to the hypothesis that PTMC could provide an adequate barrier against postoperative adhesions when placed intraperitoneally.

To evaluate the efficacy of PTMC film (Flexisurge Adhesion Barrier, Medisse BV, Ede, The Netherlands) as an antiadhesive material, we compared this material with 2 commercially available antiadhesive therapies (Seprafilm and Adept), and a control group in a rat adhesion model. We hypothesize that the PTMC film provides adequate adhesion prevention, at least comparable with that of commercially available therapies.

Because abdominal surgery involves resection of parts of the bowel, it should be investigated if the use of the PTMC film is safe in the presence of gastrointestinal anastomoses. The concept that an equilibrium exists between collagen synthesis and lysis, which can result in either adhesion formation or anastomotic leakage, is widely accepted.[19] Furthermore, the presence of a foreign body, persistent infection, or trauma can cause adhesions.[20] Therefore, it was crucial to examine whether the PTMC film would still be effective in an infected milieu, without aggravating the infection. In this study, we investigated potential risks associated with the use of the PTMC film both in the presence of a colonic anastomosis and in the case of polymicrobial sepsis in an experimental rat model.

MATERIALS AND METHODS

Materials. PTMC was polymerized by ring opening polymerization of 1,3-trimethylene carbonate (For You Medical, P.R. China). Subsequently, the PTMC polymer was compression molded into films. Films produced had an average thickness of 150 μm. Sterilization was performed under inert atmosphere using gamma radiation. An A-B-A PTMC–polyethylene glycol (PEG)–PTMC triblock copolymer was synthesized by ring opening polymerization of 1,3-trimethylene carbonate using PEG (Sigma Aldrich, St Louis, MO) as initiator.

Commercially available products of HA-CMC (Seprafilm) and icodextrin 4% (Adept Adhesion Reduction Solution, Baxter, Utrecht, The Netherlands) were purchased and used according to the manufacturer's instructions. Before surgery, HA-CMC sheets were cut into 5 × 7-cm patches under sterile conditions. The experimental PTMC sheets were provided as individually packed sterile films measuring 9 × 6 cm and were cut to a size of 5 × 7 cm before operation.

Animals. Ninety adult male Wistar rats (Harlan, Horst, The Netherlands) with a body weight of 200–250 g were housed at the Central Animal Facilities of the Maastricht University. Male rats were chosen because their anatomy allows scrotal fat to form adhesions quite easily. Furthermore, studies have showed that female hormones can affect adhesion formation.[21,22] Animals were cared for according to local standards and were provided with free access to food and water. The experimental protocol complied with the Dutch Animal Experimental Act and was approved by the Ethical Committee of Animal Experiments.

Study design. The experiment was divided into 3 parts. In the first part, the efficacy of the PTMC film was compared with commercially available antiadhesion products (n = 44; n = 11 per group) with a follow-up of 14 days:

- Group 1 was implanted with the PTMC film. This film was fixed intraperitoneally with the tacky copolymer

layer directed toward the visceral organs. To prevent migration of the film; additional fixation of the corners to the abdominal wall using 4 polyglactin 4-0 sutures was applied.
- Group 2 had the HA-CMC film implanted intraperitoneally. Application of the film was done according to the manufacturer's instructions.
- Group 3 received an intraperitoneal dose of 5 mL icodextrin 4%, which corresponds with 1.5 L in an adult male subject weighing 75 kg.
- Group 4 had no material implanted and was considered the control group.

In the second part, the effect of the PTMC film on a colonic anastomosis was investigated ($n = 26$; $n = 13$ per group), and in the third part a cecal ligation and puncture model was used to compare infection rate between the PTMC group and a control group ($n = 20$; $n = 10$ per group). Follow-up was 7 days in both high-risk studies.

Operative procedure efficacy study. Before surgery, all animals received a subcutaneous injection of 0.05 mg/kg buprenorphine. Anesthesia was induced with isoflurane 5% and maintained with isoflurane 2.5%. The abdomen was shaved and disinfected, and the animals were placed in the supine position. A 5- to 6-cm midline incision was performed, through which the abdomen was accessed. Ischemic buttons were created according to the technique described by Rajab et al.[23] In short, musculoperitoneal tissue was lifted using surgical forceps after which a suture was run through the base of the button. A ligature was made on 1 side of the button, followed by a similar ligature around the complete base of the button. Using this technique, 6 buttons were created in each animal, 3 on each side of the midline. The buttons had a diameter of approximately 0.5 cm, and were spaced 1 cm apart (Fig 1).[23,24] Subsequently, a 1 × 1-cm portion of the tip of the cecum was abraded using a sterile cotton swab until petechial lesions occurred.[25,26] After humane killing with an inhalation overdose of carbon dioxide, the abdomen was opened through an H-shaped incision along the old midline incision, and toward the flanks caudal and cranial of the ischemic buttons. Care was taken to avoid dissection through the ischemic buttons or through existing adhesions. The amount of adhesions to the ischemic buttons, midline, cecum, or sutures was scored macroscopically.

Operative procedure safety study. A rat model for colonic anastomosis was used in which the abdominal cavity was accessed through a 5-cm craniocaudal midline incision of the skin and abdominal musculature. The cecum was identified and placed on sterile gauzes hydrated with sterile saline solution to prevent dehydration. The colon was transected 2 cm distal from the cecum and an end-to-end anastomosis was created using 12 interrupted polypropylene 6/0 sutures (Prolene, Ethicon, Johnson & Johnson, Somerville, NJ; Fig 2, *A*), after which the intestines were repositioned into the abdominal cavity and the PTMC film was implanted and fixed to the abdominal wall.

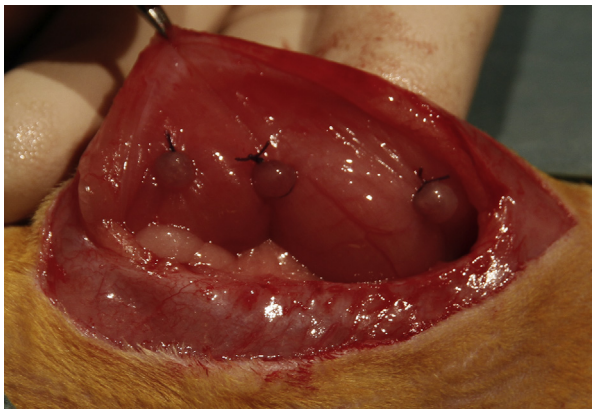

Fig 1. Three ischemic buttons were created on each side of the abdominal wall.

To induce a controlled infection cecal ligation and puncture was performed as described previously.[27,28] In this model, the cecum was manipulated carefully outside the abdominal cavity and ligated just distal to the ileocecal valve with a monofilament nonabsorbable suture (4/0 Ethilon; Ethicon, Johnson & Johnson), maintaining the continuity of the bowel. The cecum was punctured distally to the ligation with an 18-G needle. No PTMC film was implanted during the initial operation. After 1 day, animals underwent relaparotomy to assess the extent of infection using peritoneal swabs and place a PTMC film in animals in the PTMC group.

For means of hydration a bolus of 2 mL of sterile saline solution was injected subcutaneously. In all experiments, the abdominal wall was closed using an absorbable running suture of polyglactin 4-0 (Vicryl; Ethicon, Johnson & Johnson). The skin was closed intracutaneously with a running suture of polyglecaprone 4-0 (Monocryl; Ethicon, Johnson & Johnson).

Adhesion scoring. Adhesions to buttons were scored by 2 independent observers. The number of buttons with adhesions present was recorded. Data were presented as mean number of buttons with adhesions. Adhesions to the abraded cecum and midline were recorded in a similar fashion.

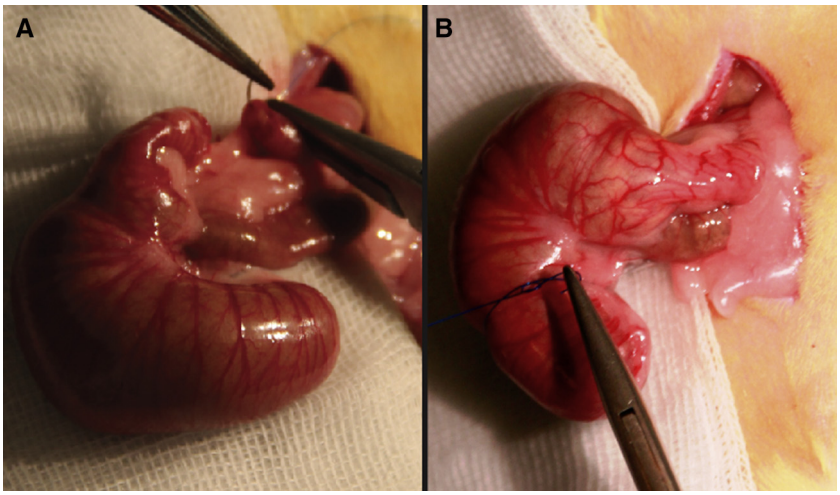

Fig 2. Safety of PTMC in the abdominal cavity was investigated using an anastomotic leakage model (*A*) and a cecal ligation and puncture model (*B*).

Examination of anastomotic leakage. Anastomotic leakage was graded on a scale from 0 (no anastomotic leakage), 1 (small abscess at the anastomotic site < 1 cm^3), 2 (large [>1 cm^3] abscess at the anastomotic site), 3 (fecal pollution of the abdomen), to 4 (complete dehiscence with peritonitis). Adhesions at the anastomotic site were evaluated in a blinded fashion according to the scoring scale of van der Ham et al.[29]

After humane killing, the anastomotic segment was resected and paraffin-embedded sections were prepared. Sections were stained with hematoxylin and eosin using standard histologic techniques. Specimens were randomly scored according to the 0–4 Ehrlich and Hunt numerical scale as modified by Phillips et al.[30]

Bursting pressure. A 5-cm segment of intestine including the anastomosis with and adherent organs was resected en bloc. The colon distal of the anastomosis was clamped, and a plastic tube was inserted in the proximal end and ligated with a single polyglactine 4/0 suture (Vicryl, Ethicon). Each anastomosis was immersed in 1× phosphate-buffered saline, air was infused using a pressure device attached to a manometer (IDEE, Maastricht University, Maastricht, The Netherlands) and pressure was manually increased by inflating the colon with air. The bursting pressure of the anastomosis was defined as the intraluminal pressure at which air leakage was initially observed from the anastomosis (mBar).

Infection rate. At day 1, 1 day after the cecal ligation and puncture, the abdomen was reopened through the midline incision, and a culture swab of the abdominal cavity was obtained to confirm fecal peritonitis. At day 7, animals were humanely killed and culture swabs were taken to measure infection. Swabs were analyzed using broad-range 16S ribosomal RNA gene polymerase chain reaction for detection and identification of bacterial pathogens. Furthermore, plasma was collected with a cardiac puncture to perform a blood culture to check for sepsis.

Statistical analysis. All data concerning adhesions are expressed as median with range. Normality tests using the Kolmogorov–Smirnov test were performed. Nonparametric data were analyzed using the Kruskal–Wallis test. In case of significance, the difference was confirmed by the Mann–Whitney test, followed by a Bonferroni post hoc test. For categorical data, a Fisher's exact test was performed. Statistical analyses were performed using Prism 5.0 for Mac (Graphpad Software, Inc, San Diego, CA) and SPSS 20.0 for Mac (SPSS Inc, Chicago, IL).

RESULTS

Two animals died during follow-up in the efficacy study. One animal from group 3 died preoperatively, possibly owing to an overdose of anesthetic. Another animal from group 1 died 5 days after the initial operation; this was owing to severe sepsis caused by leakage of bowel content through a cecal perforation. All other animals showed a normal postoperative recovery. In the safety studies, all animals completed the 7-day follow-up. Welfare of animals in both the efficacy and safety studies was assessed using extensive scoring, but no humane endpoints were reached

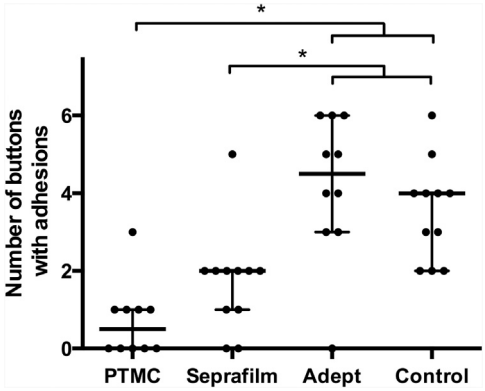

Fig 3. Number of buttons with adhesions per group. Data are presented as median values ± interquartile range. *$P < .008$. *PTMC*, Poly(trimethylene carbonate).

and no differences were found between intervention and control groups.

Macroscopic evaluation. The PTMC films showed no signs of degradation after 14 days and could be explanted at killing. The film was still in situ in all of the surviving animals. Contrary to PTMC, the icodextrin and HA-CMC were completely resorbed after 14 days. None of the surviving animals in the efficacy study showed macroscopic signs of infection or severe inflammatory reaction. In the safety studies, signs of inflammation and discomfort were found, but were equivalent in the PTMC and control groups.

The use of a PTMC film reduces adhesion formation. PTMC films had the lowest number of adhesions to ischemic buttons of all studied groups with a median of 0.5 (range, 0–3) buttons per animal. This difference was significant compared with the control group (median, 4; range, 2–6) and the icodextrin group (median, 4.5; range, 0–6; $P < .001$), but not to the HA-CMC implant group (median 2; range, 0–5; $P = .04$). Results of adhesion formation to the ischemic buttons are presented in Fig 3 and Supplementary Fig 1.

Adhesions in the PTMC and HA-CMC groups seemed to be mostly filmy and of omental and scrotal fat origin. None of these adhesions required aggressive or sharp dissection. No adhesions of visceral organs to the buttons were found in these groups. In contrast, the control and icodextrin groups showed more pronounced dense adhesions. These adhesions required more aggressive blunt and sharp dissection. Adhesions of liver, cecum, and small intestine to the ischemic buttons were recorded in addition to the usual fatty adhesions in these groups.

The use of sutures to fix the PTMC to the abdominal wall, however, seems to increase the risk of undesirable adhesions to these sutures. Although the film seems to protect the ischemic buttons from adhesions forming to these buttons, the sutures are not protected. All 11 animals in the PTMC group had adhesions present attached to sutures fixing the film. These adhesions were denser and more difficult to dissect than those to the ischemic buttons in the same animals. Furthermore, most adhesions to ischemic buttons in this group seemed to be closely related to adhesions formed to these sutures.

No differences were found in the amount of adhesions adhered to the abraded cecum. In all but the PTMC group, 4 out of the total 11 animals have some sort of adhesion toward the abraded cecum. In the PTMC group only 2 animals showed adhesions toward the cecum. No differences were found between the groups using Fisher's exact test (Supplementary Fig 2, *A*).

Equal anastomotic leakage in both PTMC and control group. We found no higher anastomotic leakage rate in the PTMC group (3/13) compared with the control group (4/13; $P = 0.99$; Supplementary Fig 2, *D*); the severity of anastomotic leakage did not differ between groups ($P = .695$; Supplementary Fig 2, *C*). The anastomoses in the PTMC group needed higher pressure to burst (249 ± 14.2 vs 195 ± 22.0 mBar; Supplementary Fig 2, *B*; $P = .067$). Microscopically, no differences were found between experimental groups.

No differences in infection rate between experimental groups. Bacterial load at day 7 did not differ between PTMC (3.1×10^8 copies/μL; interquartile range, $1.0\times10^6 - 9.8\times10^{10}$) and control groups ($8.1\times10^8$ copies/μL; interquartile range $2.1\times10^8 - 3.1\times10^9$; $P = .35$; Supplementary Fig 2, *E*). There were no differences in the frequency of positive versus negative blood cultures between groups ($P = .637$; Supplementary Fig 2, *F*).

DISCUSSION

In this study, we investigated a new antiadhesive barrier composed of PTMC (co)polymers and compared it with commercially available antiadhesive therapies. Prevention of intraperitoneal adhesions remains an integral part of daily surgery practice.[6] Postoperative adhesions are known to have a devastating impact on quality of life and increases the risk for reoperations.[31] Even though the use of minimally invasive techniques seems to reduce the risk of adhesion formation, this is not sufficient to adequately prevent all postoperative adhesions, indicating there is still need for additional adhesion prevention.[1,15,32,33]

PTMC is a highly biocompatible and versatile material with highly favorable characteristics.[34,35] Contrary to currently available materials, the PTMC film degrades by surface degradation, not by bulk degradation. This difference allows the material to retain its mechanical characteristics and provide prolonged separation of adhering tissues.[34-36] Furthermore, degradation of PTMC induces only mild inflammatory reaction, leading to the hypothesis that intraperitoneal placement of PTMC film gives a reduction of postoperative adhesions comparable with or even better than commercially available materials.[34]

The results of this experiment indicate PTMC film (FlexiSurge Adhesion Barrier) does lead to a significant reduction in the amount of adhesions. The fact that the PTMC results are comparable to HA-CMC (Seprafilm), which is also a solid film, indicates that physical barriers are an effective way to prevent adhesions. As a more slowly degrading material, PTMC provides long-term and effective separation of tissues, because its degradation happens through surface erosion. This reduction is significant compared with the control group, indicating the application of a physical barrier is beneficial in adhesion prevention.

Surprisingly, the liquid adhesion barrier did not lead to a reduction in the number of adhesions. Although human trials are inconclusive,[37] icodextrin (Adept) does seem to be effective in several other studies.[8,38]

Furthermore, there are experimental studies indicating that icodextrin is also effective in rat models, showing less adhesion formation compared with Ringers lactate.[13,39] However, in these studies icodextrin solution was either provided in higher volumes or in greater concentrations, possibly allowing the liquid to remain effective for longer periods of time. It is assumed that the reason for a reduced effectiveness in rats is the presence of α-amylase in the peritoneal fluid of rats, leading to a faster resorption of the icodextrin fluid, reducing the duration the fluid remains present in the abdominal cavity.[13,40] This could have resulted in the ineffectiveness of the fluid in our study.

Another strong aspect of the new PTMC film is its handling. In contrast with the HA-CMC film, PTMC is highly flexible with sufficient tensile strength, allowing for easy positioning and repositioning within the first few minutes after implantation,[18,34] whereas the HA-CMC film is reported to be brittle, sticky, and difficult to apply, limiting its use in surgical practice.[15,41] Furthermore, the HA-CMC barrier was completely resorbed in all animals after the 14 days follow-up, whereas the PTMC film kept its structural integrity at least until day 14. Although peritoneal wound healing is completed after 7–10 days, the HA-CMC material loses its structural integrity within the first 24 hours by turning into a hydrophilic gel.[14,42,43] Because the PTMC material degrades through surface erosion, it may provide adequate tissue separation for a longer period of time.[16,34]

Because damage to the mesothelial lining and the subsequent fibrotic response are considered to be key components in adhesion formation, the main focus of adhesion prevention should lie within the first 7–10 days.[14,42] For this reason, we think a follow-up of 14 days provides adequate information on the effect of PTMC barrier on adhesion prevention. Beside, after 14 days, the presence of an intact barrier shows PTMC exceeds the duration of protection of both HA-CMC and icodextrin.

Although adhesion formation can have long-term, detrimental effects on the quality of life of patients, in some cases adhesion formation is necessary, for example, for in anastomotic healing. It has been shown that certain antiadhesive products may predispose to peritonitis and anastomotic dehiscence.[11,44] To address this issue, we placed PTMC film in both the presence of a colonic anastomosis as well as in a model for controlled infection. In both models, the presence of the PTMC film did not cause any increase in anastomotic leakage rate, nor did it aggravate the induced infection. We did not compare PTMC with the other products, because they are already available on the market and therefore have been tested for safety. Furthermore, because there were no differences between PTMC and control, there are no risks involved in using PTMC in an infected abdomen in a rat model.

Unfortunately, at the time of writing, PTMC film required suture fixation to maintain adequate positioning throughout the follow-up. Although the PTMC reduced the number of adhesions to the ischemic buttons significantly, unprotected sutures fixing the film seemed to induce adhesion formation at this site. The need for sutured fixations was one of the limitations for practical PTMC film application. Before the film can be tested in a clinical setting, the fixation strength of an attached, tacky copolymer layer should be sufficient to provide sutureless fixation.

Another limitation of this study is a possible lack of power to detect any significant differences in number of adhesions to the cecal abrasion. Although the results of PTMC films are excellent

for the adhesions to the ischemic buttons, the effectiveness in preventing adhesions in other locations in the abdomen could not be shown in this model. However, there still seems to be a small, albeit not significant, reduction in the cecal adhesion formation, which could have clinical implications in larger groups.

In conclusion, a new PTMC film with a tacky PTMC-PEG layer is effective in reducing postoperative adhesions to the abdominal wall in a rat ischemic button model. Furthermore, the use of this film does not compromise anastomotic healing or peritonitis. The proven efficacy and safety in this preclinical study, along with the easy handling of the PTMC film make it a promising new prevention tool in postoperative adhesions. Further research is necessary to elucidate whether these results are also valid in humans.

Funding for acquisition of materials and animals was kindly provided by Medisse BV, Ede, The Netherlands.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2015.02.004.

REFERENCES

1. Lower AM, Hawthorn RJ, Clark D, Boyd JH, Finlayson AR, Knight AD, et al. Adhesion-related readmissions following gynaecological laparoscopy or laparotomy in Scotland: an epidemiological study of 24 046 patients. Hum Reprod 2004;19:1877-85.
2. Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, et al. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet 1999;353:1476-80.
3. Parker MC, Wilson MS, van Goor H, Moran BJ, Jeekel J, Duron JJ, et al. Adhesions and colorectal surgery – call for action. Colorectal Dis 2007;9:66-72.
4. Nieuwenhuijzen M, Reijnen MM, Kuijpers JH, van Goor H. Small bowel obstruction after total or subtotal colectomy: a 10-year retrospective review. Br J Surg 1998;85:1242-5.
5. Rajab TK, Wallwiener M, Talukdar S, Kraemer B. Adhesion-related complications are common, but rarely discussed in preoperative consent: a multicenter study. World J Surg 2009;33:748-50.
6. Ellis H, Crowe A. Medico-legal consequences of post-operative intra-abdominal adhesions. Int J Surg 2009;7:187191.
7. Schreinemacher MH, Broek ten RP, Bakkum EA, van Goor H, Bouvy ND. Adhesion awareness: a national survey of surgeons. World J Surg 2010;34:2805-12.
8. Broek ten RP, Stommel MW, Strik C, van Laarhoven CJ, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. Lancet 2014;383:48-59.
9. Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. Cochrane Database Syst Rev 2009:CD005080.
10. Metwally M, Watson A, Lilford R, Vandekerckhove P. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev 2006: CD001298.
11. Fazio VW, Cohen Z, Fleshman JW, van Goor H, Bauer JJ, Wolff BG, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. Dis Colon Rectum 2006;49:1-11.
12. Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, et al. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev 2008: CD000475.
13. Wallwiener M, Brucker S, Hierlemann H, Brochhausen C, Solomayer E, Wallwiener C. Innovative barriers for peritoneal adhesion prevention: liquid or solid? A rat uterine horn model. Fertil Steril 2006;86:1266-76.
14. Boland GM, Weigel RJ. Formation and prevention of postoperative abdominal adhesions. J Surg Res 2006; 132:3-12.
15. Brochhausen C, Schmitt VH, Planck CN, Rajab TK, Hollemann D, Tapprich C, et al. Current strategies and future perspectives for intraperitoneal adhesion prevention. J Gastrointest Surg 2012;16:1256-74.
16. Pêgo AP, Van Luyn MJ, Brouwer LA, van Wachem PB, Poot AA, Grijpma DW, et al. In vivo behavior of poly(1,3-trimethylene carbonate) and copolymers of 1,3-trimethylene carbonate with D,L-lactide or epsilon-caprolactone: degradation and tissue response. J Biomed Mater Res A 2003;67:1044-54.
17. Van Leeuwen AC, Huddleston Slater JJ, Gielkens PF, de Jong JR, Grijpma DW, Bos RR. Guided bone regeneration in rat mandibular defects using resorbable poly(trimethylene carbonate) barrier membranes. Acta Biomater 2012; 8:1422-9.
18. Van Leeuwen AC, Van Kooten TG, Grijpma DW, Bos RR. In vivo behaviour of a biodegradable poly(trimethylene carbonate) barrier membrane: a histological study in rats. J Mater Sci Mater Med 2012;23:1951-9.
19. Hendriks DT, Mastboom WJ. Healing of experimental intestinal anastomoses. Dis Colon Rectum 1990;33: 891-901.
20. Lauder CI, Garcea G, Strickland A, Maddern GJ. Abdominal adhesion prevention: still a sticky subject? Dig Surg 2010;27: 347-58.
21. Bozkurt S, Yuzbasioglu MF, Bulbuloglu E, Gul M, Kale IT. Prevention of postoperative peritoneal adhesions by administration of estrogen. J Invest Surg 2009;22:263-7.
22. Kaya U, Oktem M, Zeyneloglu HB, Ozen O, Kuscu E. Impact of aromatase inhibitors on adhesion formation in a rat model. Fertil Steril 2007;87:934-9.
23. Rajab TK, Wauschkuhn CA, Smaxwil L, Kraemer B, Wallwiener M, Wallwiener CW. An improved model for the induction of experimental adhesions. J Invest Surg 2010; 23:35-9.
24. Rajab TK, Smaxwil L, Wallwiener M. Animal model for local pharmacotherapy in adhesion prophylaxis–a proof of concept. J Invest Surg 2013;26:200-3.
25. Chaturvedi AA, Lomme RM, Hendriks T, van Goor H. Prevention of postsurgical adhesions using an ultrapure alginate-based gel. Br J Surg 2013;100:904-10.
26. Lalountas MA, Ballas KD, Skouras C, Asteriou C, Kontoulis T, Pissas D, et al. Preventing intraperitoneal adhesions with atorvastatin and sodium hyaluronate/carboxymethylcellulose: a comparative study in rats. Am J Surg 2010; 200:118-23.

27. Hubbard WJ, Choudhry M, Schwacha MG, Kerby JD, Rue LW, Bland KI, et al. Cecal ligation and puncture. Shock 2005;24(Suppl 1):52-7.
28. Deerenberg EB, Mulder IM, Ditzel M, Slieker JC, Bemelman WA, Jeekel J, et al. Polyvinyl alcohol hydrogel decreases formation of adhesions in a rat model of peritonitis. Surg Infect (Larchmt) 2012;13:321-5.
29. van der Ham AC, Kort WJ, Weijma IM, Jeekel H. Transient protection of incomplete colonic anastomoses with fibrin sealant: an experimental study in the rat. J Surg Res 1993; 55:256-60.
30. Phillips JD, Kim CS, Fonkalsrud EW, Zeng H, Dindar H. Effects of chronic corticosteroids and vitamin a on the healing of intestinal anastomoses. Am J Surg 1992;163:71-7.
31. Broek ten RP, Issa Y, van Santbrink EJ, Bouvy ND, Kruitwagen RF, Jeekel J, et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. BMJ 2013;347:f5588.
32. Schnüriger B, Barmparas G, Branco BC, Lustenberger T, Inaba K, Demetriades D. Prevention of postoperative peritoneal adhesions: a review of the literature. Am J Surg 2011; 201:111-21.
33. Broek ten RP, Kok-Krant N, Bakkum EA, Bleichrodt RP, van Goor H. Different surgical techniques to reduce postoperative adhesion formation: a systematic review and meta-analysis. Hum Reprod Update 2013;19:12-25.
34. Bat E, van Kooten TG, Harmsen MC, Plantinga JA, van Luyn MJ, Feijen J, et al. Physical properties and erosion behavior of poly(trimethylene carbonate-co-ε-caprolactone) networks. Macromol Biosci 2013;13:573-83.
35. Zhang Z, Kuijer R, Bulstra SK, Grijpma DW, Feijen J. The in vivo and in vitro degradation behavior of poly (trimethylene carbonate). Biomaterials 2006;27:1741-8.
36. Bat E, Van Kooten TG, Feijen J, Grijpma DW. Macrophage-mediated erosion of gamma irradiated poly (trimethylene carbonate) films. Biomaterials 2009;30:3652-61.
37. ten Broek RP, Stommel MW, Strik C, van Laarhoven CJ, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. Lancet 2013;383:48-59.
38. Tepetes K, Asprodini EK, Christodoulidis G, Spyridakis M, Kouvaras E, Hatzitheofilou K. Prevention of postoperative adhesion formation by individual and combined administration of 4 per cent icodextrin and dimetindene maleate. Br J Surg 2009;96:1476-83.
39. Klink CD, Schickhaus P, Binnebösel M, Jockenhoevel S, Rosch R, Tolba R, et al. Influence of 4% icodextrin solution on peritoneal tissue response and adhesion formation. BMC Surg BioMed 2013;13:34.
40. van den Tol P, Raa ten S, van Grevenstein H, Marquet R, van Eijck C, Jeekel H. Icodextrin reduces postoperative adhesion formation in rats without affecting peritoneal metastasis. Surgery 2005;137:348-54.
41. Ward BC, Panitch A. Abdominal adhesions: current and novel therapies. J Surg Res 2011;165:91-111.
42. Hellebrekers BW, Kooistra T. Pathogenesis of postoperative adhesion formation. Br J Surg 2011;98:1503-16.
43. Brochhausen C, Schmitt VH, Rajab TK, Planck CN, Kraemer B, Wallwiener M, et al. Intraperitoneal adhesions–an ongoing challenge between biomedical engineering and the life sciences. J Biomed Mater Res A 2011;98: 143-56.
44. Tang C-L, Jayne DG, Seow-Choen F, Ng Y-Y, Eu K-W, Mustapha N. A randomized controlled trial of 0.5% ferric hyaluronate gel (Intergel) in the prevention of adhesions following abdominal surgery. Ann Surg 2006;243:449-55.